Global optimization in nonlinear models: optimization and evolution in metabolic networks

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GOALS

- Understand fine tuning of metabolic processes in the adaptive response to stress
  - Develop a method for understanding the evolution of these responses.
    - Use mathematical models (GMA models) for evaluating system response
  - Optimization methods may help.
    - Develop an efficient method for GMA models
  - Hypothesis: Biological adaptation occurs in feasible regions constrained by physiological requirements.
    - Develop a computational method for identifying such feasible regions.

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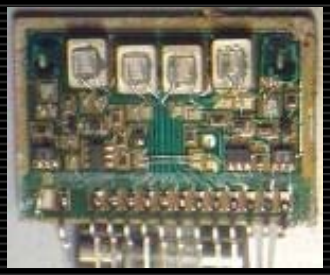
Optimization vs. evolution: Understanding adaptive responses

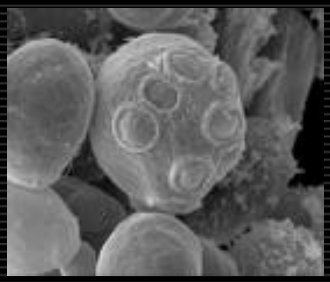
Physiological constraints that shape adaptive responses

- Adaptive responses require a fine tuning of metabolic processes
  - Increase flux, limit metabolite accumulation, limit energy waste, assure appropriate time scale, robustness.

- Optimization: Which is the optimal change in enzyme levels so that a maximum (minimum) is attained with these criteria (for instance, minimize cost while obtaining an appropriate increase in flux and a limited increase in metabolite levels) Biotechnological applications (*engineered design*)



- Evolution: Find the feasible changes in enzyme levels compatible with a set of restrictions. These may (or may not) optimize a given criteria Understand evolution (*emergent design*)



Vilaprinyó, E, Alves R, Sorribas A (2006) Use of physiological constraints to identify quantitative design principles for gene expression in yeast adaptation to heat shock. BMC Bioinformatics 7:184

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Optimization in GMA models
Improvement of existing methods

- The original problem is a non-convex nonlinear programming problem (NLP).

- Take advantage of the power-law formalism:
  - Decompose the problem into two hierarchical levels: a master Mixed Integer Linear Programming (MILP) problem and a slave Non-Linear Programming (NLP) problem (Bergamini et al., 2005; Polisetty et al., 2008; Guillen-Gosalbez & Sorribas, 2009).
  - The power-law structure provides a natural way for obtaining a useful MILP using piecewise linear approximations on logarithmic transformations.
  - The master MILP provides an underestimation of the minimum, while the slave NLP produces an overestimation.
  - Convergence to the global maximum is guarantied.

Guillén-Gosálbez G, Sorribas A (2009) Identifying quantitative operation principles in metabolic pathways: a systematic method for searching feasible enzyme activity patterns leading to cellular adaptive responses. BMC Bioinformatics **10:**386

Identification of feasibility regions in GMA models

Optimization methods provides an optimum (either a maximum or a minimum of an objective function) solution.

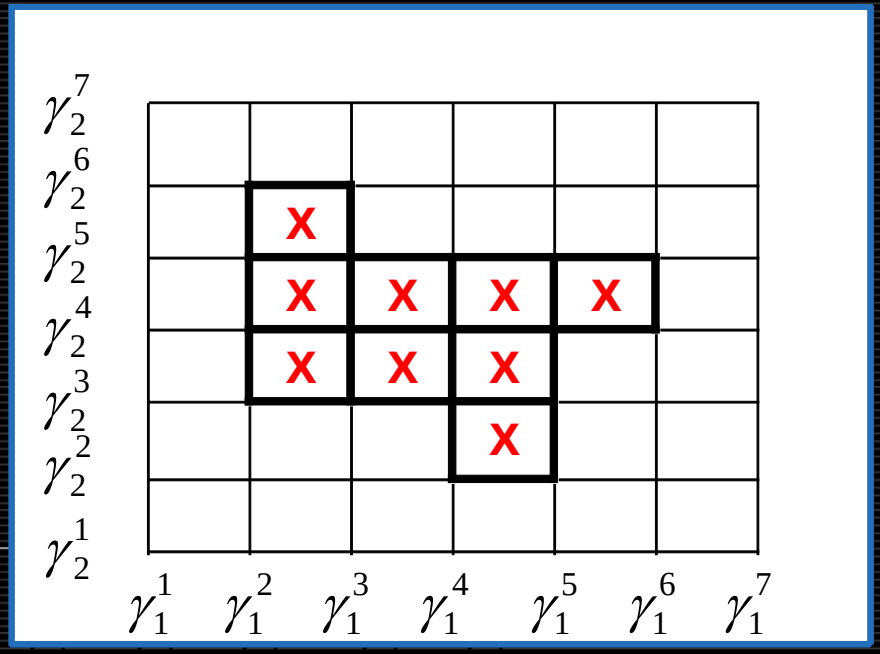
(Constrained) Optimal solutions may be different from actual adaptive responses.

Evolutive adaptations are found in feasible regions.

METHOD

- Find the global maximum.
- Identify the hyper-rectangle that contains the maximum.
- Iterate, excluding the previous hyper-rectangle.
- Continue until no feasible solution is found.
- Refine the search within the feasible region.

Simple example with two parameters



Guillén-Gosálbez & Sorribas (2009)
BMC Bioinformatics **10:**386

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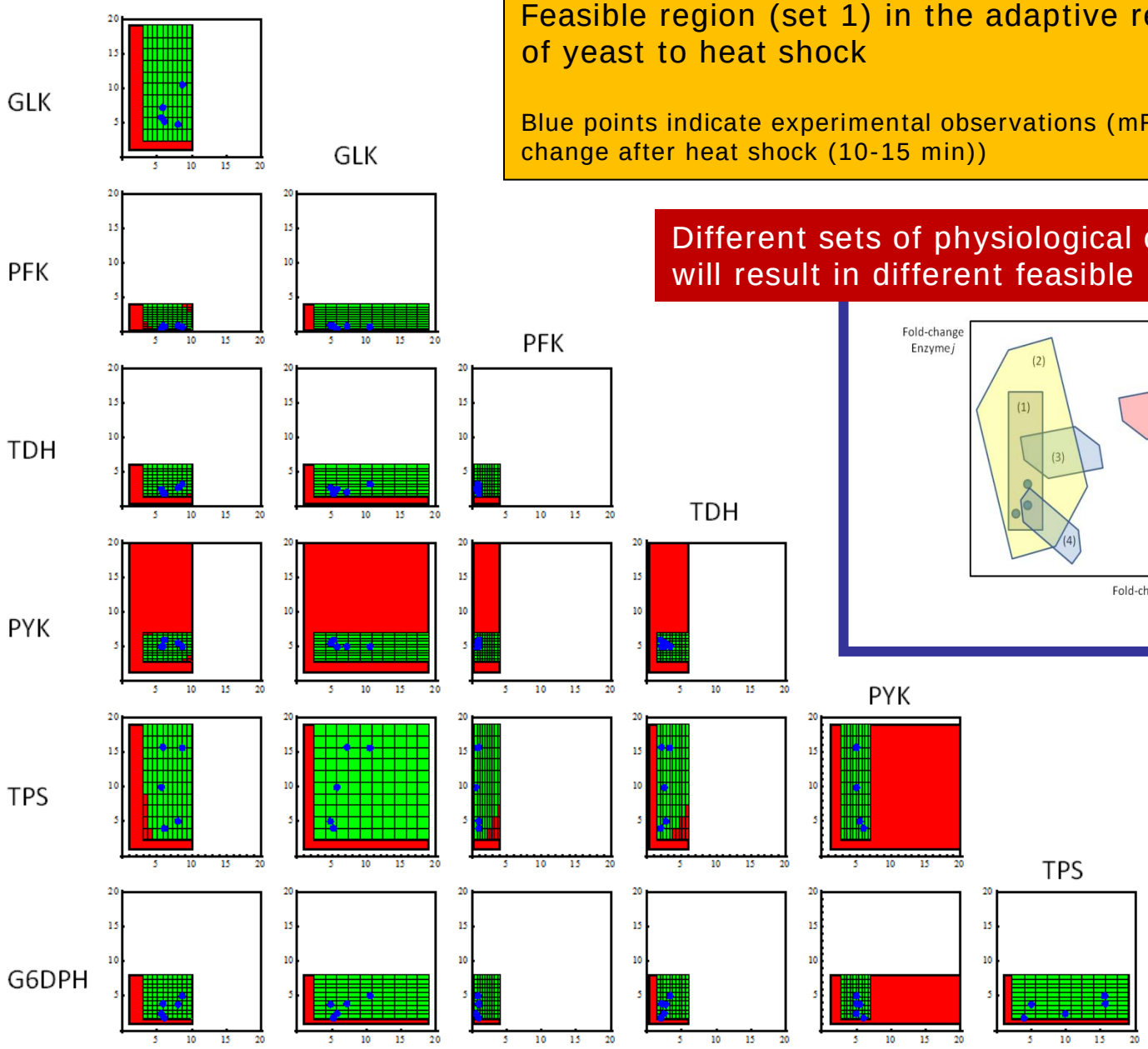
Set 1 defines a feasibility region that contains the experimental data

Feasible region (set 1) in the adaptive response of yeast to heat shock

Blue points indicate experimental observations (mRNA fold change after heat shock (10-15 min))



Different sets of physiological constraints will result in different feasible regions

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Conclusion

- A global optimization method for non-linear models in GMA has been developed.
- The method is efficient for large models.
- Through recasting techniques, this method provides a global optimization methods for any non-linear problem.
- Feasibility analysis is straighforward and allows understanding adaptive responses in cellular metabolism.
- Implementation of these techniques in user-friendly programs is a next step.

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